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High Rates of Obstructive Sleep Apnea Symptoms Among Patients With Schizophrenia

Aniyizhai Annamalai, M.D., Laura B. Palmese, Psy.D., Lydia A. Chwastiak, M.D., M.P.H., Vinod H. Srihari, M.D., Cenk Tek, M.D.

Background: *Patients with schizophrenia have high rates of obesity and cardiovascular morbidity, which are strongly associated with obstructive sleep apnea (OSA). The prevalence and risk factors for OSA are not well studied in patients with schizophrenia.* **Objective:** *The purpose of this study was to evaluate the frequency of OSA symptoms in a sample of outpatients with schizophrenia.* **Methods:** *This cross-sectional study was a secondary analysis of data generated from an insomnia study that evaluated 175 outpatients with schizophrenia or schizoaffective disorder in a single, large urban community mental health center. Results of scales evaluating insomnia were used to complete the STOP questionnaire, which is a screening tool for OSA validated in surgical populations. Appropriate statistical analysis was done to compare participants across groups.* **Results:** *Patients were classified into high risk for OSA (STOP ≥ 2) (57.7%), and low risk for OSA (STOP score < 2) (42.3%). We also identified patients with a known diagnosis of OSA (14.9%). Patients with diagnosed OSA had significantly higher STOP scores (mean 2.7 vs. 1.6 [$t = 6.3$; $p < 0.001$]). Only 23.8% of patients in the high-risk group were diagnosed with OSA. Body mass index was significantly higher in the diagnosed group ($F[2,169] = 25$; $p < 0.001$) as was diabetes ($\chi 2$ [2, $N = 175$] = 35, $p < 0.001$).* **Conclusion:** *A large number of outpatients with severe mental illness are at high risk for OSA. The STOP questionnaire is easy to use and appears to have a very high clinical utility to detect OSA. Based on our findings, further studies are warranted to validate the tool in patients with severe mental illness.*

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INTRODUCTION

Patients with schizophrenia and other chronic mental illnesses lose potential decades of life as compared with people without serious mental illness. Most of this premature mortality is due to chronic medical conditions, such as heart disease, cancer, cerebrovascular, and pulmonary diseases.[1] Patients with serious mental illness have a higher prevalence of cardiovascular risk factors such as obesity, diabetes, hypertension, and hyperlipidemia[2] for which they are screened and treated less often than their peers in the general population.[3]

Obesity, which is common amongst those with serious mental illness, is also a strong risk factor for obstructive sleep apnea (OSA).[4,5] OSA is also associated with an increased risk for cardiovascular morbidity and mortality,[6–8] and this provides a strong rationale to screen for and treat OSA in patients with serious mental illness.

OSA is a sleep disorder characterized by oxygen desaturation during sleep that affects between 2% and

Received January 3, 2014; revised February 23, 2014; accepted February 24, 2014. From Department of Psychiatry, Yale School of Medicine, New Haven, CT (AA, LBP, VHS, CT); Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA (LAC). Send correspondence and reprint requests to Aniyizhai Annamalai, M.D., Department of Psychiatry, Yale School of Medicine, 34 Park St, New Haven, CT 06519; e-mail: Aniyizhai.annamalai@yale.edu

7% of the general population.[7,9] It is best diagnosed by overnight polysomnography and is defined by the apnea hypopnea index, which is the number of hypopnea and apnea events divided by the number of hours of sleep. Mild, moderate, and severe OSA is defined as a apnea hypopnea index of 5–15, 16–30, and >30, respectively.[4] Continuous positive airway pressure (CPAP) is highly efficacious for treatment of OSA but the adherence rate is low.[10]

OSA is a novel target for cardiovascular and pulmonary risk reduction among patients with schizophrenia. Patients with schizophrenia have a high prevalence rate of chronic obstructive pulmonary disease[11]; OSA is more common in patients with chronic obstructive pulmonary disease and is associated with worse clinical outcomes in those patients.[12] Moreover, OSA is also associated with cognitive deficits such as attention, executive function, and memory,[13–15] and there is some evidence that treatment of OSA leads to remediation of deficits in attention and vigilance.[14] This is especially salient as cognitive impairment is a core feature of schizophrenia, which often predicts psychosocial functioning.[16] Exacerbation of preexisting deficits by OSA constitutes a significant concern.

The prevalence of OSA and its risk factors among individuals with schizophrenia is not known. Among 364 psychiatric inpatients referred for sleep disorder consultation, patients with schizophrenia were found to have a higher prevalence of OSA (57.1% women and 46.2% men) than those with other diagnoses.[17] In another study of 52 geriatric patients with schizophrenia, the prevalence of sleep-disordered breathing (measured as a respiratory disturbance index >10) was estimated at 48%.[18] Takahashi et al.[19] found a rate of sleep-related respiratory disorder (measured as a desaturation index of ≥ 5 on overnight pulse oximetry) to be 21.9% for men and 13.5% for women among 101 inpatients diagnosed with schizophrenia. The latter 2 studies tested unselected patients who had not been identified as having any sleep-related breathing disorders.

Identification of those who are at high risk is the first step in addressing this issue. Although polysomnography is the gold standard for the diagnosis of OSA, it is not feasible or useful as an initial screening tool as it is time consuming, expensive to administer, and not readily available at typical outpatient facilities. The aims of this study were (1) to evaluate the prevalence of OSA symptoms among a sample of patients with schizophrenia at a community mental health center and (2) to evaluate STOP as a screening tool for OSA among patients with schizophrenia.

METHODS

This study was the second stage of a cross-sectional evaluation of 175 patients with schizophrenia or schizoaffective disorder who participated in a study evaluating insomnia.[20] These patients were recruited from an urban community mental health center and completed the Insomnia Severity Index (ISI) and Pittsburg Sleep Quality Index (PSQI) scales. The study protocol was approved by the Yale University Human Investigation Committee and all participants provided written informed consent.

For the secondary study, results of ISI and PSQI scales were used to assess for OSA symptoms and further data analysis done to determine risk correlates.

The following measures were used to evaluate insomnia and associated factors:

1. Body mass index (BMI) was calculated for all patients with standard equation: weight in kg/height in m^2.
2. Depression symptom severity: Calgary Depression Scale is a standard depression scale used in the assessment of depression in patients with schizophrenia.[21]
3. Schizophrenia symptom severity: Clinical Global Impression of Severity-Schizophrenia version is a brief semistructured form in which the rater indicates their global impression of severity of several domains of schizophrenia.[22]
4. Insomnia was evaluated using the ISI, a brief sleep questionnaire used to screen for insomnia. The scoring classifies patients into 4 categories ranging from "no insomnia" to "severe insomnia."[23] The PSQI used to measure subjective sleep quality ranges from 0–21 with a score >5 indicating sleep difficulties.[24]
5. Cognitive impairment: Digital symbol substitution test (DSST) is a subtest of the Wechsler Adult Intelligence Scale-III that measures processing speed.[25] It has been shown to be the strongest predictor of global cognitive impairment in schizophrenia across studies.[26]
6. Patients were also asked about demographic characteristics, and co-existing medical conditions (diabetes, hypertension, and hyperlipidemia). Quality of life was evaluated using the Quality of

Life Enjoyment and Satisfaction Questionnaire—abbreviated version for schizophrenia (QLES-Q-18), a quality of life measure validated for patients with schizophrenia.[27]

7. History of diagnosis and treatment of OSA: Patients were asked about a history of testing or treatment for sleep apnea, and adherence with treatment if prescribed (currently using CPAP—yes/no). All patient medical records were reviewed to verify presence or absence of OSA diagnosis.

Next, screening for OSA symptoms was performed as described here. Patients were defined as high or low risk for OSA based on STOP questionnaire. The STOP screening instrument for OSA has been validated in surgical populations and was found to have a high internal validity.[28,29] In primary care settings, it is more likely to identify OSA than routine questioning by physicians.[30] The instrument has a high sensitivity and specificity in surgical populations, but it is more sensitive in detecting moderate to severe OSA: for an apnea hypopnea index cutoff value greater than 5, the sensitivity is 65.6% and specificity is 60%; with an apnea hypopnea index greater than 30 as the cutoff, the sensitivity and specificity are 79.5% and 48.6%, respectively.[28] STOP is an easy-to-use tool that takes less than 1 minute for a primary care physician or psychiatrist to administer. The 4 questions are as follows:

- Snoring—"Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?"
- Tiredness—"Do you often feel tired, fatigued or sleepy during daytime?"
- Observed pauses in breathing—"Has anyone observed you stop breathing during your sleep?"
- Blood Pressure—"Do you have or are you being treated for high blood pressure?"

Each question on the STOP questionnaire is assigned 1 point. A score of less than 2 on STOP is low risk for OSA and a score of 2 or more is high risk, thus indicating the need for further evaluation for OSA by polysomnography.

Individual items from the ISI and PSQI were used as a proxy for items on the STOP questionnaire to develop a modified STOP tool. The ISI question "To what extent do you consider your current sleep problem to cause daytime fatigue?" was used as a substitute for the "Do you often feel tired, fatigued or sleepy during the day" on STOP. The PSQI item "How often have you had trouble sleeping because you cough or snore loudly" was used as a substitute for "Do you snore loudly (louder than talking or heard through closed doors)" on STOP. The PSQI item "Has your bed partner said you have had long pauses between breaths while asleep" substituted for "Has anyone observed you stop breathing during your sleep" item on STOP (Table 1).

STOP BANG is a screening instrument that has higher specificity and sensitivity in surgical populations. BMI, age, neck circumference, and gender are evaluated in addition to the 4 questions in STOP. A score of 3 or more on STOP BANG is considered high risk for OSA. As neck circumference was not available for this population, a modified version without the neck circumference (STOP BAG) was calculated and the same cutoff score of 3 or higher was used to classify participants as high risk. Modified STOP BAG scores were compared with the modified STOP scores to determine if diagnostic utility of the screening tool was enhanced.

Statistical Analysis

Univariate analysis of variance was calculated to compare 3 groups: participants with a diagnosis of OSA, those at low risk for OSA (modified STOP < 2),

TABLE 1. Comparison of STOP and Modified STOP

	STOP questions	Modified STOP questions
Snoring	Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	How often have you had trouble sleeping because you cough or snore?
Tiredness	Do you often feel tired, fatigued or sleepy during daytime?	To what extent do you consider your current sleep problem to cause daytime fatigue?
Observed pauses in breathing	Has anyone observed you stop breathing during your sleep?	Has your bed partner said you have had long pauses between breaths while sleeping?
Blood pressure	Do you have or are you being treated for high blood pressure?	Do you have or are you being treated for high blood pressure?

and those at high risk (modified STOP $\geq$ 2) with respect to several measures including BMI. Post hoc analysis included the Bonferroni correction. The chi square and multinomial logistic regression tests were used when appropriate to compare the different groups. Pearson correlation was used to compare modified STOP and STOP BAG. A $p < 0.05$ significance level was used for all analyses.

RESULTS

Demographic and clinical characteristics of our sample are as shown in Table 2. These 175 community mental health center outpatients with schizophrenia were predominantly men; 44% met the clinical criteria for insomnia based on ISI scores; 61.6% participants were obese (BMI $\geq$ 30 kg/m^2); mean BMI of participants was 33.7 kg/m^2; 24% had diabetes, 31.4% had hypertension; and 21.7% had hyperlipidemia. Mean Calgary Depression score was 4.7; clinical global impression of severity-schizophrenia version overall mean severity was 3.7. The overall mean score on the QLES was 59.3.

Overall, 26 participants (14.9%) reported having been previously diagnosed with OSA. Treatment was prescribed for half[13] of the 26 patients diagnosed with OSA. There was no available information on treatment for the other 13 patients. Rate of treatment compliance with CPAP was 53.8% among those who were prescribed treatment (7/13 patients), based on self-report of any use of CPAP.

TABLE 2. Sample Characteristics (n = 175)

Age (mean)	43.7 (SD = 9.9)
Gender	
Male (%)	57.1
Female (%)	42.9
BMI (kg/m^2, mean)	33.7 (SD = 8.8)
Diabetes (%)	23.4
Hypertension (%)	31.4
Hyperlipidemia (%)	21.7
Medications	
Atypical antipsychotics (%)	71.5
Typical antipsychotics (%)	19.4
Both (%)	9.1
Insomnia*	
Clinical (%)	48
Subthreshold (%)	35
Diagnosed with OSA (%)	14.9
High risk for OSA (STOP $\geq$ 2)	44
Low risk for OSA (STOP < 2)	41.1

SD = standard deviation; BMI = body mass index; OSA = obstructive sleep apnea.

* Classification based on score on first 7 items of ISI (8–14: subthreshold insomnia; >15: clinical insomnia).

A total of 101 patients (57.7%) were classified as high risk (modified STOP $\geq$ 2) and 74 (42.3%) as low risk (modified STOP < 2). Among participants who did not report a diagnosis of OSA, 77 (51.7%) were classified as high risk for OSA and 72 (48.3%) as low risk. Further analysis was done comparing 3 groups—diagnosed OSA, low risk by modified STOP, high risk by modified STOP. There were significant differences in mean BMI between the 3 groups (those with diagnosed OSA; those at high risk by modified STOP, and those at low risk by modified STOP) ($F(2, 169) = 25; p < 0.001$). A post hoc Bonferroni analysis showed significant difference between the diagnosed and low-risk groups (42.8 vs 31.3) as well as the diagnosed and high-risk groups (42.8 vs 32.9); there was no statistically significant difference between the mean BMI in the low- and high-risk groups. The prevalence of hypertension, diabetes, and hyperlipidemia in each group is shown in Table 3. There was a significant difference between the 3 groups in prevalence of hypertension $\chi^2(2, N = 175) = 40, p < 0.001$; diabetes, $\chi^2(2, N = 175) = 35, p < 0.001$; and hyperlipidemia, $\chi^2(2, N = 175) = 8.2, p = 0.01$. A multinomial logistic regression showed a statistical difference in hypertension between all 3 groups; diabetes between diagnosed and both other groups; hyperlipidemia only between low-risk and diagnosed groups. These differences remained significant even when controlling for BMI. There were no differences between the 3 groups regarding age, gender, or type of antipsychotic used (typical, atypical, or both). There were also no significant differences across these groups with respect to mean depression symptom severity, schizophrenia symptom severity, or quality of life.

Mean DSST raw score was significantly different ($F(2, 169) = 3.1; p = 0.01$) between the groups. A post hoc Bonferroni analysis showed significant difference between low- and high-risk groups (41.7 vs 36.5) but when controlled for age, the difference was no longer significant; there was no statistically significant difference between the diagnosed group and either the low-risk or high-risk groups.

When the low-risk group (excluding the 2 cases who had a diagnosis of OSA) was compared with the entire high-risk group (including undiagnosed and

TABLE 3. Medical Conditions by Group

	Low risk (STOP < 2)*, $N = 72$	High risk (STOP ≥ 2)*, $N = 77$	Diagnosed OSA, $N = 26$
BMI (mean)	31.3 (SD = 7.4)	32.9 (SD = 6.5)	42.8 (SD = 9)
Hypertension			
Yes (%) ($n = 55$)	6.9	41.6	69.2
No (%) ($n = 120$)	93.1	58.4	30.8
Hyperlipidemia			
Yes (%) ($n = 38$)	12.5	24.7	38.5
No (%) ($n = 137$)	87.5	75.3	61.5
Diabetes mellitus			
Yes (%) ($n = 42$)	12.5	19.5	69.2
No (%) ($n = 133$)	87.5	80.5	30.8

OSA = obstructive sleep apnea; BMI = body mass index; SD = standard deviation.

* Patients without a known diagnosis of OSA.

diagnosed), significant difference was seen between mean BMI in both the groups ($F(2,169) = 6.3$; $p = 0.02$). There was no difference in mean DSST scores.

Patients with a diagnosis of OSA had significantly higher modified STOP scores (mean 2.7 vs 1.6 ($t = 6.3$; $p < 0.001$)) than those who did not. Among patients with a diagnosis of OSA, 92.3% ($n = 24$) were high risk according to modified STOP score criteria (≥ 2), indicating a high sensitivity of STOP in diagnosing OSA in this population. However, of all the patients classified as high risk in our sample, only 23.8% had been previously diagnosed with OSA.

When modified STOP BAG scores were used, among participants who did not have a diagnosis of OSA, 67 (45%) were classified as low risk (modified STOP BAG < 3) and 82 (55%) as high risk (modified STOP BAG ≥ 3). Hence, in the sample with no OSA diagnosis, more participants were classified as high risk with STOP BAG than with STOP. Among those with a diagnosis of OSA, 24 of 26 patients (92.3%) were classified as high risk, which was the same as with STOP. The agreement between modified STOP and modified STOP BAG was 88% in the total sample and 100% in the sample with an OSA diagnosis. There was a high correlation between modified STOP and modified STOP BAG ($r = 0.83$, $N = 175$, $p < 0.001$).

DISCUSSION

There was a high prevalence of OSA (14%) among this sample of outpatients with schizophrenia, and a large number of patients (44%) who had not been diagnosed with OSA were at high risk for OSA based on screening using a modified STOP questionnaire. These rates are high compared with rates previously reported in the general population (ranges from 2%–7%).[31] Among patients in this sample who were diagnosed with OSA, self-reported adherence with CPAP treatment was low (50%)—but comparable with rates reported in the general population of between 46% and 83%.[10]

In numerous previous studies, obesity was the single most significant predictor of OSA.[4,7] In our sample, BMI was significantly higher in the group with an OSA diagnosis (compared with those who did not report a diagnosis or treatment for OSA). Interestingly, among patients who did not have an OSA diagnosis, there was no significant difference in the mean BMI of those at high risk for OSA compared with those at low risk. It is possible that patients with a higher BMI have more severe OSA symptoms increasing the likelihood of referral for diagnostic sleep studies. Other cardiovascular risk factors tended to be higher in people with diagnosed OSA. This group was significantly more likely to have diabetes compared with both other groups. Hypertension is a known complication of OSA and is included as a screening question in STOP; as expected, the prevalence is higher in the diagnosed and high-risk groups. The group with diagnosed OSA has the highest number of cardiovascular risk correlates.

Cognition is affected in both OSA and schizophrenia. However, in our sample, there was no difference in the DSST between the diagnosed group and either the low-risk or high-risk groups; there was a difference in raw scores between the low-risk and high-risk groups, but this did not remain significant after adjustment for age. It is possible that cognitive

impairment of schizophrenia is masking that induced by OSA. A more detailed cognitive battery may discern possible differences.

Our findings suggest that OSA may be significantly underdiagnosed among those with schizophrenia. Low rates of screening may result from a lack of awareness by psychiatric practitioners that their patients are at increased risk of OSA and of the adverse outcomes associated with untreated OSA. Rates of screening and diagnosis of OSA are also low in the general population, especially among patients who do not manifest overt signs of OSA such as excessive sleepiness.[31] The condition can present in a variety of ways and clinical impression alone has poor sensitivity and specificity.[32] Hence, there should be a low threshold for referring patients for polysomnography and STOP can be used as an initial screening tool.

In our study, 92.3% of patients who had a diagnosis of OSA screened as positive on modified STOP indicating a high sensitivity for this screening tool among individuals with schizophrenia. Although polysomnography test results were not available for these patients, their diagnosis was verified by a review of their medical records. It is known from previous studies that sensitivity of the STOP tool is higher for those with more severe symptoms. In this study population, it is likely that the patients diagnosed with OSA were referred for polysomnography because of severe symptoms. A significant portion of the patients who did not carry a diagnosis of OSA appeared to have high risk. It is possible that OSA rates would be even higher if these patients were screened.

The clinical utility of a screening tool depends on the prevalence of the disorder being tested. Previous reports of OSA prevalence in schizophrenia have varied widely. Given the variability of prevalence and the fact that the number of patients with a truly negative screening for OSA in the sample is not known, predictive validity of STOP screening cannot be inferred. A limitation of this study is that specificity cannot be reliably calculated, as data regarding true negativity for OSA is not available.

STOP BAG has higher sensitivity and specificity as a screening tool in the general population. But STOP is quick, practical, and easier to administer within the constraints of a time-limited psychiatric assessment. Previous studies have shown poor rates of measurement of waist circumference by providers in mental health treatment settings even though it is recommended for antipsychotic drug monitoring.[33] It is even less likely that providers will consistently measure neck circumference. And nonmedical professionals provide many services in community mental health centers. Furthermore, in our sample of patients with an OSA diagnosis, clinical utility was not improved by using STOP BAG.

OSA increases cardiovascular risk, affects quality of life, and is associated with cognitive deficits. Multidisciplinary strategies for prevention, diagnosis, and treatment of OSA in the severely mentally ill population are warranted. Given the high rate of nonadherence with CPAP treatment, primary prevention (by targeting obesity) may be more effective in reducing the incidence of and the complications from OSA. In addition, assessment and treatment of other metabolic conditions would reduce overall cardiovascular morbidity.

LIMITATIONS

STOP scores were derived from similar questions in other tests and so a modified STOP tool was used. However the questions were very similar (Table 1). Patient self-report of OSA was used to calculate the clinical utility of STOP in the small sample of patients with a known diagnosis; however, this was verified by the diagnosis on the medical records. Sample size was relatively small. Though there is a significant association of STOP scores with an OSA diagnosis, we were not able to calculate the specificity of a modified STOP as a screening tool as polysomnography was not done on the sample classified as low risk by modified STOP. We were unable to determine factors predictive of nonadherence with the recommended treatment of CPAP, as the number was too small.

Although the DSST is the best predictor of cognitive deficits in schizophrenia,[26] it may not have been effective at identifying subtle changes in an already impaired population.

CONCLUSIONS

There is a high prevalence of OSA symptoms among patients with schizophrenia. Only a small number of patients are screened for OSA. Once diagnosed, treatment adherence is also low. STOP is a brief,

easy-to-use screening tool for OSA in individuals with severe mental illness. It can be used by medical and nonmedical professionals. A positive screen should lead to further testing with the gold standard diagnostic test, polysomnography. Further research is needed to validate the STOP questionnaire in this vulnerable population and to increase the understanding of risk factors for OSA and nonadherence with treatment. Primary prevention by targeting obesity may be the most effective (and cost-effective) strategy to reduce the comorbidity associated with OSA among individuals with severe mental illness.

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